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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/441,140	11/16/1999	BEKA SOLOMON	27/150	3910

1444 7590 08/22/2003

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	18

DATE MAILED: 08/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/441,140	SOLOMON, BEKA	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 126-149* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 126-149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12 13 14* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *17* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment filed 22 August 2002 (Paper No. 15) has been received and entered in full. Claims 5-9, 16-25, and 88-125 have been cancelled. Claims 126-149 have been added.

2. The substitute Declaration filed Paper No. 11 has been entered.

3. Currently claims **1-4** and **126-149** are under examination.

4. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Withdrawn Objections And/Or Rejections

5. The rejection of claims **1-4** as being based upon a defective reissue Declaration under 35 U.S.C. §251 as set forth at pp. 2-5 ¶3-6 in the previous Office Action (Paper No. 8, 29 June 2001) is withdrawn in view of Applicant's filing of a replacement Declaration (Paper No. 11, being entered).

6. The rejections of claims **5-125** as set forth in the previous Office Actions (Paper No. 4, 5 September 2000; Paper No. 8, 29 June 2001) are *moot* in view of Applicant's cancellation of the claims.

New Objections And/Or Rejections

7. The Specification is objected to because there is a typed correction next to the abstract as filed ("[molecules]" and then typed next to this is "involves" typed over something covered in white-out). This correction or alteration has not been entered as an amendment.

8. The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

9. Claims **1-4** and **126-149** are rejected as being based upon a defective reissue declaration under 35 U.S.C. 251. See 37 CFR 1.175. The nature of the defect is set forth below.

10. In accordance with 37 CFR 1.175(b)(1), a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1) must be received before this reissue application can be allowed. The reissue oath/declaration filed with this application is defective (see 37 CFR 1.175 and MPEP § 1414) because of the following: a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1) must be filed with all amendments to the reissue application prior to allowance. No such supplemental reissue oath/declaration was filed in conjunction with the claims amendment of Paper No. 15 filed 22 August 2002.

11. Receipt of an appropriate supplemental oath/declaration under 37 CFR 1.175(b)(1) will overcome this rejection under 35 U.S.C. 251. An example of acceptable language to be used in the supplemental oath/declaration is as follows:

> "Every error in the patent which was corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention on the part of the applicant."

12. Claims **126-149** are rejected under 35 U.S.C. 251 for lack of defect or error in the original patent and as not being an error correctable by reissue. The claims to the methods, "a method of preventing or reducing aggregation of β-amyloid" (claims 130-133), "a method for

disaggregating an aggregate of β-amyloid" (claims 134-137), "a method for treating a subject afflicted with Alzheimer's disease" (claims 138-141), "a method of preventing or reducing aggregation of β-amyloid in a subject" (claims 142-145), and "a method of disaggregating an aggregate of β-amyloid in a subject" (claims 146-149), were considered nonelected in the original application as a result of a restriction requirement, and applicant failed to further prosecute these claims in a divisional application timely filed under 35 U.S.C. 121. Failure to timely file a divisional application including non-elected claims is a deliberate act and not error in the prosecution of the original patent. *In re Orita*, 193 USPQ 145.

13. Applicant accepted issuance of the original patent with its claims to a single elected invention. It is noted that:

"By acquiescing in the examiner's restriction requirement, and failing to file divisional applications on the subject matter of the non-elected claims, applicant foreclosed (because that was not error) his right to claim that subject matter. If it were not error to forego divisional applications on subject matter to which claims had been made in the original application, it cannot on the present record have been error to forego divisional applications on subject matter to which claims had never been made." *In re Weiler,* 229USPQ 673 at 677.

14. In addition, the MPEP states:

"A reissue applicant's failure to timely file a divisional application is not considered to be error causing a patent granted on elected claims to be partially inoperative by reason of claiming less than the applicant had a right to claim. Thus, such error is not correctable by reissue of the original patent under 35 U.S.C. 251. *In re Watkinson*, 900 F.2d 230, 14 USPQ2d 1407 (Fed. Cir. 1990); *In re Orita*, 550 F.2d 1277, 1280, 193 USPQ 145, 148 (CCPA 1977). See also *In re Mead,,* 581 F. 2d 251, 198 USPQ 412 (CCPA 1978). Likewise, if the original patent specification or the prosecution history of the original patent shows an intent not to claim the newly presented invention, that invention cannot be added by reissue. In these situations, the reissue claims should be rejected under 35 U.S.C. 251 for lack of defect in the original patent and lack of error in obtaining the original patent. See also MPEP § 1412.01." (MPEP 1450)

15. The Examiner acknowledges that this rejection may be seen as incongruous with the agreement reached and summarized in the Interview Summary (Paper No. 12.5, 14 August 2002)

wherein the Applicant agreed to submit a new set of simplified claims, reducing the number of inventions and species for initial examination on the merits. This interview was taken into consideration and the decision was made that the instant claims are directed to the same invention of claim 24 of the parent application (Application No. 08/358786) while only differing in scope. This is evident from the Applicant's intent to correct the error of not filing the broad treatment claims (oath/declaration) and the presence of the broad claims in this application (claim 5 and 88, for example). Thus the claims as pending are not directed to patentably distinct inventions from claim 24 of parent application (Application No. 08/358786), they are only more narrow in scope. This rejection is consistent with the rejection as set forth in paragraph 7 of Office Action No. 8 (29 June 2001).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims **126-129** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

17. The above invention is drawn to a pharmaceutical composition comprising an anti-β-amyloid antibody or an antigen binding fragment thereof, wherein said antibody and fragment are effective to prevent or reduce aggregation of β-amyloid or disaggregate β-amyloid

aggregates in a subject. The language of said claims encompasses both *in vivo* and *in vitro* use of the claimed invention.

18. The Specification provides examples of how monoclonal antibodies, CP_{10} and CP_9, specific for Carboxypeptidase A (CPA) inhibit temperature induced denaturing as measured by enzymatic activity (Figures 3 and 4). No assays were performed to confirm that the denatured protein was in fact "aggregated" as heat may denature but not necessarily cause aggregation. Also, CPA was not "disaggregated" by either CP_{10} and CP_9. Furthermore it is entirely possible that the antibodies (CP_{10} and CP_9) did not prevent or inhibit aggregation *per se*, but worked to inhibit the unraveling of the CPA protein folding, "holding" critical enzymatic domains in place as to allow for the maintenance of enzymatic activity. It is also noted that "prevention" is understood in the art to mean a total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The specification does not demonstrate total prevention.

19. Figures 5 and 6 concern antibody binding to CPA, while it is not doubted that said antibodies (CP_{10} and CP_9) bind CPA, it is questioned whether this data supports the claims.

20. Figure 7 shows an Aβ aggregation assay performed with two anti-β-antibodies, 6F/3D. Firstly, no evidence is presented in the instant application nor the post filing publication by the Inventor to support the limitation of "disaggregation" of Aβ aggregates because the assay includes a step of centrifugation to remove aggregated Aβ prior to the ELISA assay (Col. 13 lines 27-30 and "MATERIALS AND METHODS" of Solomon *et al.* (January 1996) "Monoclonal antibodies inhibit *in vitro* fibrillary aggregation of the Alzheimer β-amyloid

peptide." PNAS **93**: 452-455). Therefore no prevention was achieved as aggregated β-amyloid was removed.

21. Secondly, the monoclonal antibody 6F/3D had no discernable effect on the β-amyloid aggregates as noted in Solomon *et al.* (Figure 1B) and the instant Specification (Figure 7B). Third, the AMY-33 monoclonal antibody did not show any disaggregation effect or prevention of aggregation as discussed above. Also Solomon *et al.* (1996) notes that: "The mAb AMY-33 did not exhibit a similar inhibitory effect on metal-induced amyloid aggregation." (pp. 454) Both Zn and Al are known to be present in physiological conditions thus casting doubt on the *in vivo* utility of either monoclonal antibody.

22. In addition, all the assays performed to support the claim of prevention, disaggregation, and inhibition of aggregation of Aβ using both the AMY-33 and 6F/3D monoclonal antibodies utilize either A495 or "Fluorescence Intensity" both of which are relative and not quantitative measurements. Therefore no conclusive statement can be supported regarding the percentage of prevention, disaggregation, and inhibition of aggregation of Aβ using either the AMY-33 and 6F/3D monoclonal antibodies based on a relative measurement. Further, the protocol used by the Applicant discards "aggregated β-amyloid" after initial 3 hour incubation. Thus it is not clear as to the efficiency of either AMY-33 or 6F/3D in prevention, disaggregation, or inhibition of aggregation of Aβ since no comparison was made between the amount of Aβ that remained soluble versus the amount that aggregated and was discarded {Col. 13 lines 27-30 and "MATERIALS AND METHODS" of Solomon *et al.* (January 1996)}.

23. With regard to *in vivo* use of anti-aggregation antibodies, neither the Specification nor the prior art provides any support to correlate unrelated proteins with the prevention, disaggregation,

or inhibition of aggregation with an alleviation of symptoms or providing some relief to the patient.

24. While the specification prophetically considers antibodies that may prevent or reduce aggregates or disaggregate aggregates in patients, the instant Specification does not provides sufficient guidance that would enable a skilled artisan to conceive of and make any antibody that would prevent or reduce aggregation or disaggregate aggregates in a subject. Absent guidance and sufficient disclosure to adequately overcome obstacles of a therapeutic method, the endeavor to make the desired antibody is unpredictable and would require an undue amount of experimentation.

25. The claims, however, are drawn very broadly to antibodies and antigen binding fragments thereof capable of preventing or reducing β-amyloid deposits or disaggregate β-amyloid aggregates. Since the specification fails to provide any guidance for the successful isolation or characterization of such a claimed antibody capable of prevention or reduction of β-amyloid plaques or disaggregation of β-amyloid aggregates in patients and since resolution of the various complications in β-amyloid aggregation makes the art highly unpredictable, one of skill in the art would have been unable to make the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of dosages, evaluation of effectiveness, and possibly new diagnosis methods as the only current method of examining β-amyloid plaques involves immunocytochemistry (see US 6399314 B1). While immunocytochemistry of mouse brains is readily practiced in the art, it is a hurdle that must be overcome to successfully practice

the invention to its full scope in humans. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. The factors listed below have been considered in the analysis of enablement:

(A) **The breadth of the claims;**
(B) **The nature of the invention;**
(C) **The state of the prior art;**
(D) **The level of one of ordinary skill;**
(E) **The level of predictability in the art;**
(F) **The amount of direction provided by the inventor;**
(G) **The existence of working examples; and**
(H) **The quantity of experimentation needed to make or use the invention based on the content of the disclosure.**

26. The following references are cited herein to illustrate the state of the art of β-amyloid.

27. On the state of the prior art, Walker *et al.* (July 1994) "Labeling of Cerebral Amyloid In Vivo with a Monoclonal Antibody." Journal of Neuropathology and Experimental Neurology **53**(4): 377-383 teaches the administration of a monoclonal anti-β-amyloid antibody (10D5) into the cerebrospinal fluid of aged monkeys (pp. 377). Following injection, the monkeys were sacrificed and their brains examined to confirm that the antibodies injected labeled Aβ plaques (Figures 1-5). It is noted that the monoclonal anti-β-amyloid antibody (10D5) did not disaggregate, prevent, or inhibit Aβ aggregation.

28. Concerning the nature of the invention, Pan *et al.* (September 2002) "Antibodies to β-Amyloid Decrease the Blood-to-Brain Transfer of β-Amyloid Peptide." Exp. Biol. Med. **227**(8): 609-615 teaches that the administration of anti-β-amyloid antibodies to PDAPP mice decreases the incidence of β-amyloid plaques not through disaggregation but through decreasing the

concentration of β-amyloid in the central nervous system. This reference demonstrates that the apparent prevention or disassembly of β-amyloid aggregates or fibrils can be actually due to a decrease amount of β-amyloid in an area of the animal or patient. Thus the β-amyloid plaques are not disassembled or prevented *per se*, but their formation is inhibited or in another sense, slowed.

29. Moreover on the nature of the invention, of the two anti-β-amyloid antibodies disclosed in the instant Specification, Akiyama *et al.* (15 February 1999) "Occurrence of the diffuse amyloid beta-protein (Abeta) deposits with numerous Abeta-containing glial cells in the cerebral cortex of patients with Alzheimer's disease." Glia **25**(4): 324-331 teaches that 6F/3D does not readily bind Aβ plaques in cerebral cortex samples from an Alzheimer's patient. Thus the skilled artisan is presented with evidence contrary to the claim that 6F/3D will bind naturally occurring aggregates, the first step in "disaggregation".

30. On the breadth of the claims, the instant Specification does not provide any evidence of disassembly or disaggregation, both of which are active processes. To fulfill the requirements as set forth by the preamble, the claimed method's antibody must overcome thermodynamic driving forces (van der Waals) which push the hydrophobic residues towards the water poor environment of the inner amyloid, allowing for more thermodynamically favorable microstates for the amino acid side groups to occupy. When taking into consideration the structure and nature of amyloid fibers as discussed by Perutz *et al.* (16 April 2002) "Amyloid fibers are water-filled nanotubes." PNAS **99**(8): 5591-5595 this is unlikely (pp. 5595). It is more reasonable to attribute the lower fibril incidence to inhibition or slowing but not to active processes of disassembly.

31. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to make the claimed antibodies. Additionally, a person skilled in the art would recognize that predicting the efficacy of making an antibody *in vivo* based solely on its prophetic considerations and desired properties as highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of making the claimed antibody for *in vivo* therapeutic regiments, such a disclosure would not be considered enabling since the state of β-amyloid aggregation and anti-β-amyloid antibodies is highly unpredictable.

Summary

32. Claims **1-4** and **126-149** are hereby rejected.

33. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
August 20, 2003

Gary L. Kunz

GARY KUNZ
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